UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,448	06/04/2001	Patrick Midoux	USB98ASIDM	3117

466 7590 02/10/2005

YOUNG & THOMPSON
745 SOUTH 23RD STREET
2ND FLOOR
ARLINGTON, VA 22202

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,448	MIDOUX ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-26 and 28-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *20-26, 28-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 11/8/04.

Claim 27 was canceled as requested.

Claims 20-26 and 28-35 remain pending and are under consideration in this Office Action.

Claim Objections

Claims 20 is objected to because it recites "A positively charged oligomeric conjugate positively charged". The second instance of "positively charged" should be deleted. Similarly the phrase "comprising monomeric components" should be deleted from the phrase "monomeric components comprising monomeric components having substituted NH_3^+."

Claim 30 stands objected to. It is suggested that, in the phrase "and/or in a cell nucleus", the word "into" should be substituted for the word "in".

Claim 33 is objected to because the last instance of "a" should be "an".

Claim 35 is objected to because the phrase "comprising monomeric components" should be deleted from the phrase "monomeric components comprising monomeric components having substituted NH_3^+." It is redundant. One of the two instances of "wherein" immediately before and after "a)" should be deleted. Insertion of the word "wherein" in item '(b)' was unnecessary and is ungrammatical. The word "are" should be inserted between the words "and" and "selected" in item 'b)'. The words "midazoles", "quinalines", and "pysidines" are misspelled.

Response to Arguments

Applicant's arguments filed 11/8/04 have been fully considered as the apply to the objections above, but they are not persuasive.

Applicant asserts at page 15 of the response that "in" was replaced by "into" in claim 30. This is incorrect, "in" has not been replaced by "into", and the objection is maintained.

Comment

It is unclear what is the use of the limitation in claim 20 requiring that the protonable residues "contain a functional group enabling them to be linked to said oligomer". In the claim, the protonable groups only exist in a form that ***is already*** linked to the oligomer, so there is no need for another group that allows them to be further linked to the oligomer. Also the specification does not contemplate the concept of a protonable residue twice linked to the oligomer.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-26 and 28-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 and dependents are indefinite because it is unclear what is meant by the phrase "monomeric components having substituted NH_3^+represent at least 50% by monomeric components". Also it is unclear what is the purpose in the "a)" clause of the phrase "by protonable residues" because it is not connected in any meaningful way to any other claim element. The entire "a)" clause makes no sense, and provides no meaningful basis for the remainder of the claim which is devoted to the characteristics of "protonable residues". In other words, the claim has been amended such that it now has no requirement for substituted NH_3^+ residues comprising protonable residues. As a result, the portion of the claim devoted to describing protonable residues is irrelevant and serves no purpose.

Claim 20 and dependents are indefinite because they recite in item 'b)' "at least one unsubstituted NH_3^+ group selected from the group consisting of imidazoles, quinolines, pterines, and pyridines." This clause makes no sense because none of the species of the Markush group is an unsubstituted NH_3^+. In fact, there is only one thing that is an "unsubstituted NH_3^+ group", and that is "NH_3^+".

Claim 20 and dependents are indefinite because it is unclear what is meant by the term "substituted" in the context of NH_3^+ groups. For example, regarding paragraph 2 and items a) and b), the Examiner was at first under the impression that "substituted NH_3^+ " meant that one of the H atoms of NH_3^+ had been replaced by a protonable residue. However, at item c) of claim 20 it appears that "NH_3^+ of said monomers are optionally substituted by uncharged residues" refers to the replacement of the entire NH_3^+ group, because a reduction the number of positive charges in the conjugate is

required as a result of substitution. As such it is unclear if Applicant intends in paragraph 2 and items a) and b) to replace only a hydrogen of NH_3^+, or to replace the entire NH_3^+, with a protonable residue. Similarly it is unclear if the molecules constituting a recognition signal in item d) are intended to be added onto NH_3^+, or to replace NH_3^+. As such the structure of the claimed molecules is unclear.

Claim 20 is confusing at paragraph 5 of item d) wherein it is indicated that a molecule containing a recognition signal may be added "by substitution of the NH_3^+ of said protonable residues". It is not clear what is the antecedent for "the NH_3^+". If the antecedent is the "at least one unsubstituted NH_3^+" group in paragraph 3 of item b), then the claim is confusing because it requires that this NH_3^+ must be unsubstituted, but then makes provisions for substituting it. On the other hand, if "at least one unsubstituted NH_3^+" is not the antecedent for "the NH_3^+", then "the NH_3^+" lacks antecedent basis altogether. This rejection was made in the previous Action, but Applicant did not respond to it.

Claim 25 and dependents are indefinite because it is unclear to what the terminal CO2 is bonded. The depicted bond is not attached to anything, so the structure of the claimed composition is undefined.

Claim 25 and dependents are unclear because, although they define what 'R' represents when 100% of all 'R' groups are selected from the Markush group bridging pages 5 and 6 of the amendment, they do not meaningfully define R for situations in which less than 100% of the 'R' groups are selected from that group. For example, at page 6 of the amendment, claim 25 requires that "0-50% of all R groups (corresponding

to f wherein: $0 < f \leq u$)" must be NH_3^+ or substituted NH. However, it is unclear what is the numerical value of f. The claim embraces indefinite embodiments such as when 50% of all R groups are selected from the Markush group bridging pages 5 and 6 of the amendment, and less than 50% of the R groups are selected from the Markush group bridging pages 6 and 7 of the amendment. In these situations, at least 50% of the R groups remain undefined.

Claim 25 and dependents are indefinite because all recited equations involving the quantity 'u' are invalid. The claims require that $u \geq i/2$. This sets a lower limit on the value of u, but sets no upper limit, thus the numerical value of u can increase infinitely, and far beyond the value of 'i'. So for example, the expression "i = u + j + k + h", at page 8 of the amendment, is invalid because 'u' can be greater than 'i', but the claim does not allow for negative values of j, k, and h. The expression $NH_3^+ = m = p + j + 1$ is also invalid because 'p' is defined in terms of 'u', and 'u' is indefinite. Alternatively, if one interprets m as simply the total number of NH_3^+, then the expression still fails to make sense because it requires addition of the number of alpha NH_3^+ (p) to the number of omega NH_3^+ (j), and then addition of the number '1'. It is unclear to the Examiner that there is any type of NH_3^+ in the claimed structure other than an alpha or omega NH_3^+, so it is unclear how the total NH_3^+ can be the sum of alpha and omega NH_3^+ plus 1. Further, the claims define m identically to u, i.e. $m \geq i/2$. Thus the numerical value of m must be at least half of 'i' but can increase infinitely beyond 'i'. The claims do not account for values of p and j that can be summed to give numbers that are very much larger than 'i', and certainly not infinitely larger. The expression

NH_3^+ = j + f-(k + h) is invalid for the reasons stated in the previous paragraph, i.e. 'f' is inadequately defined. The claim states that f may be equal to u, and u may be infinite, so clearly the expression is invalid.

The Examiner is gets the impression that Applicant may wish to claim a composition comprising a certain number of groups R, wherein at least half of the groups R are selected from a certain set of structures. The total number of groups R from this set of structures that is present in the composition could be represented by the quantity 'u'. The remainder of the groups R are selected from a different set of structures. The total number of groups R from this set of structures that is present in the composition could be the quantity 'f', such that the total number of groups R in the composition = u + f. If this impression is correct, then Applicant should amend the claims to make this clear.

The phrase "corresponding to a number" which appears in claims 26 and dependents, renders these claims indefinite because the nature of the correspondence is unclear. If, for example, Applicant wishes that the number of R groups in a composition should be equal to a quantity 'u', then Applicant should make this clear.

Claim 28 is indefinite because it depends from canceled claim 27.

Claims 30-32 are indefinite because the recited method steps are not concordant with the purpose set forth in the preamble. These claims are methods of intracellular transfer of oligonucleotides, but they recite no end point showing that the method is accomplished.

Claim 35 is indefinite because it is unclear what constitutes the recited ratio of "at least 50%. The claim fails to describe to what the amount of free NH_3^+ is being compared. It is also unclear what is the purpose or meaning of the phrase "by protonable residues" in item a) of the claim. As a result the remainder of the claim describing the protonable residues is irrelevant and meaningless.

Response to Arguments

Applicant's arguments filed 11/8/04 have been fully considered as they apply to the rejections set forth above, but they are not persuasive.

At page 16 of the response Applicant asserts that the term "substituted" in the context of NH3+ groups corresponds to the substitution of one of the H atoms of NH3+, and not to replacement of the entire NH3+ group, even in item 'c)'. This is unpersuasive because it is unsupported and it does not appear to make sense. In item 'c)' the result of the substitution of the NH3+ group is to decrease the number of positive charges on the oligomer by replacing a NH3+ positive charge with an uncharged residue. This would not be possible if the uncharged moiety was used to replace only an H atom of an NH3+ group, and not the entire NH3+ group. Replacement of an NH3+ H atom with an uncharged group (X) would result in an NH2-X moiety wherein the nitrogen is still positively charged because it still forms the same number of bonds. So, Applicant's explanation is not persuasive, and it remains unclear what is meant by the term "substituted" in the context of NH_3^+ groups, particularly at paragraph 2 and items a) and b) of claim 25.

Regarding the remarks set forth in the first full paragraph of page 17 of the response, it is unclear to which rejection these remarks are directed. Based on the order in which Applicant is addressing the rejections, it would appear that this paragraph is intended to address the rejection regarding a lack of antecedent basis for "the NH_3^+" of a molecule containing a recognition signal in paragraph 5 of part 'd)' of claim 20. If so, they arguments are unpersuasive because they do not address the issue of antecedent basis for "the NH_3^+". The Examiner was unable to locate any other potential response to that rejection.

Applicant asserts at page 25 that the "-" in claim 25 represents a minus sign to show that the last monomer of the oligomer terminates in a carboxylate group. In response, the PTO notes that the claim remains unclear. If Applicant intends a carboxylate group, then it would be a simple matter to amend the structure to clearly and unambiguously contain one, i.e. $C(O)O^-$, wherein the '-' is a superscript relative to the 'O'. The rejection is maintained.

At pages 17 and 18, Applicant argues that 'R' is well defined. Applicant relies on specification passages at page 9, lines 29-40, and page 10, lines 29-32 to page 11, line 16. Applicant argues at page 18, first full paragraph that when 70% of 'R' is chosen from the Markush group, then the remaining 30% is chosen from "the second group of structure" presumably at pages 10 and 11 of the specification, corresponding to those structures at pages 6 and 7 of the amended claims. However, the fact remains that the claims only define 'R' when 100% of 'R' groups are one of the recited Markush species, while the claims explicitly allow as few as 50% of 'R' groups to be these species. In

such a situation, what are the other 50% of 'R' groups? Applicant's argument is unpersuasive because the claim states that 0-50% of 'R' groups can be selected from this group, however, there is no requirement that the sum of 'R' groups selected from each group is equal to the total number of groups 'R'. In other words, Applicant's assertion that if 70% of 'R' groups are selected from the Markush group, then it follows that the remaining 30% are drawn from the second group, is unsupported. Where in the claim is the requirement that the remaining 'R' groups must come from the second group? In fact, in the claims as written the "second group" of structures is part of the Markush group referred to above, i.e. there is no second group of structures. So 50-100% of all 'R' groups must be selected from the structures set forth at page 5 line 12 to page 7, line 25 of the response. In the situation wherein les than 100% of the 'R' groups are selected from these structures, 'R' remains undefined.

At page 18 of the response, Applicant argues essentially that the claim term "u" is definite. The argument depends on to points: 1) the number "u" depends on the percentage of the residues R that are one of the structures listed for R, and 2) "u" cannot be greater than "i". This is unpersuasive. As far as the Examiner can tell, the percentage of residues R that are one of the structures listed for R is depicted as "f", not "u". See page 6 of the response. The claim states that "f" is greater than 0 and less than or equal to "u". So, it is unclear how the number "u" depends on the percentage of the residues R that are one of the structures listed for R. Further, Applicant has not pointed to any place in the claim that defines "u" as anything but "$\geq$ i/2". While Applicant argues that "u" cannot be greater than "i", the claim language clearly

contradicts this. At page 8, line 5, the claim clearly indicates that "u" may be greater than "i". For these reasons, the rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 20-24 and 29-35 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 20-24, and 29-35 are drawn to oligomers with a polymerization degree of from 5-36. The claims recite further limitations including the need for at least 50% of the monomers to comprise a substituted or unsubstituted NH_3^+, but the specification provides little further description of the backbone of the oligomer. At pages 9 and 12 the specification teaches that the backbone of the oligomer can be a hydrocarbon chain comprising peptide bonds with as many as 21 backbone carbons between each peptide bond. However, the genus of polymers that are embraced by the instant claims is far broader than this description, such that the claims as written do not provide a substantially essential structure for the backbone of the oligomer. In order to satisfy the written description requirement, one may describe a representative number of species

of the claimed genus, either by reduction to practice, drawings or description of relevant identifying characteristics. In this case, the specification has described only certain polymer structures comprising peptide bonds separated by between 1-21 saturated carbons. As such, one of skill in the art could not conclude that Applicant was in possession of the entire claimed genus at the time of the invention. The specification and the state of the prior art of record provide sufficient description of polymeric complexes comprising the oligomers with the formulas set forth in pages 9 and 12, wherein B is an imidazole, pterine, quinoline, or pyridine.

With respect to claims readable on a genus of unspecified residues that must exhibit a biological function of being protonated in a weakly acid medium and causing destabilization of cell membrane, the specification only provides sufficient description of a oligomers having a backbone of the formula as set forth in claims 25 and 26, and comprising residues having an imidazole, pterine, quinoline, or pyridine, and an NH3+ functional group, and residues having the formulae as set forth on pages 7 and 8 of the as-filed specification

With respect to claims readable on a genus of cellular recognition signals, the specification only provides sufficient description of cellular recognition signals which are peptide based recognition signal sequence, oligosaccharide based recognition signal or monosaccharide based recognition signal.

It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays for

making the polymer genus as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of oligomeric conjugates and/or functional groups thereof that must exhibit the disclosed biological functions as contemplated by the as-filed specification.

It is not sufficient to support the present claimed invention by disclosing oligomeric complexes comprising the oligomer with the formula as set forth in claims 25 and 26, wherein B is a residue with an imidazole nucleus, or a compound having the formulae as set forth on pages 6 and 7 of the as-filed specification, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any and/or all other oligomeric conjugates having other residues with the biological functions as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicant's effective filing date. Claiming all oligomeric conjugates and/or functional groups and/or recognition signals that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the

inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed oligomeric complexes that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Response to Arguments

Applicant did not specifically respond to this ground of rejection.

Enablement

Claims 20-24 and 28-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, since the claimed invention is not supported by a sufficient written description for possessing the genus of oligomeric complexes as recited in the claims, particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended, *e.g.*

functions as a nucleic acid delivery vector that exhibits all of the biological functions as recited in the claimed invention.

For example, as discussed above, the specification fails to identify a single member of the genus of "protonable residues not recognized as a recognition signal recognized by a cellular membrane receptor" even though these protonable residues are required by the claims. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of the required protonable residues cannot be overlooked as a trivial omission in the process of providing an enabling disclosure. Instead, these residues are a critical element of the claims. Because Applicant has failed to describe such residues, or to provide guidance as to how to make them, one of skill in the art would have to invent or discover them in order to make the claimed

invention. Such experimentation is undue in the absence of guidance, description, or working examples.

Response to Arguments

Applicant's arguments filed 11/8/04 have been fully considered as they apply to the rejections set forth above, but they are not persuasive.

Applicant states at page 19 of the response that claims 20-35 have been amended to further characterize the claimed complex, and that they believe that the amendment overcomes the rejection. It does not for the reasons stated above, briefly, the specification supports only the genus of oligomeric compounds set forth in claims 25 and 26.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20-26 and 33-35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Midoux et al (WO 98/22610, published 5/28/98).

WO 98/22610 was filed as PCT/FR97/02022 and is the priority document for US Patent 6,372,499. The contents of WO 98/22610 will be discussed by reference to this English language version. Midoux teaches oligomers with a polymerization degree as

low as 15, in which at least 10% of the monomers have free NH3+ groups substituted by residues that are protonable in a weak acid medium, such as histidines, pterines, quinolines, or pyridines, leading to destabilization of cell membranes. See entire document, e.g. abstract; column 4, lines 20-24; column 4, line 55 to column 5, line 40; column 6, line 48 to column 8, line 43; and column 10, line 44 to column 11, line 38. It is noted that the instant claims require at least 50% substitution. However, the recited "at least 10%" in the cited art is reasonably interpreted as embracing 10% to 100%, so the instantly claimed "at least 50%" is embraced by the range in the cited art. As such it would have been obvious to one of ordinary skill in the art to arrive at the claimed conditions through the process of routine optimization within the range in the cited art. Note that the instant application shows that the instant invention functions to deliver polynucleotides when the level of substitution is 53%. See Table 1 on page 39.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 11/8/04 have been fully considered as they apply to the rejections set forth above, but they are not persuasive.

At page 19 of the response Applicant indicates that they do not believe that there is motivation to select a degree of polymerization and a percentage of substitution of the prior art oligomers which would render obvious the instant claims because the present invention is appropriate for oligonucleotide transfection, and the prior art is directed to "DNA transfection". This is unpersuasive because the prior art teaches oligomers with a

polymerization degree as low as 15, in which at least 10% of the monomers have free NH3+ groups substituted by residues that are protonable in a weak acid medium. Thus the prior art teach a polymerization value within the claimed range. Further, the degree of substitution is reasonably interpreted as embracing 10-100%, and so overlaps the claimed range of at least 50%. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.") Furthermore it is apparent from the instant application that the instant invention functions to deliver polynucleotides when the level of substitution is 53%. As such it is clearly reasonable that in the process of optimization one of ordinary skill in the art could have reproduced a species of the instant invention, and the claims are considered obvious.

At page 20 of the response Applicant argues that the degree of polymerization and a percentage of substitution were not recognized as result effective variables, and so would not have been obvious to optimize. This is unpersuasive because 1) the cited art teaches a polymerization degree within the claimed range, thereby obviating the need for optimization of that variable, and 2) the cited art clearly shows that the

percentage of substitution affects transfection results, see e.g. Fig. 5 which shows that transfection efficiency generally increases with level of substitution. For these reasons the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20-26 and 33-35 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, and 10-15 of U.S. Patent No. 6,372,499. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-6 and 10-15 of '499 teach species of the instantly claimed genuses. As discussed above, '499 teaches at least 10% substitution of the oligomer NH3+ groups, and does not exclude substitution of 50% or greater of these groups (except in claims 7-9 which were not relied upon in this rejection). As such, the cited art clearly embraces 10% to 100% substitution, thereby rendering the instant claims obvious. See entire document, e.g. abstract; column 4,

lines 20-24; column 4, line 55 to column 5, line 40; column 6, line 48 to column 8, line 43; and column 10, line 44 to column 11, line 38. It would have been obvious to one of ordinary skill in the art at the time of the invention to arrive at the instantly claimed degree of substitution through routine optimization within the range disclosed by Midoux.

Response to Arguments

Applicant's arguments filed 11/8/04 have been fully considered as they apply to the rejections set forth above, but they are not persuasive.

At pages 20 and 21 of the response Applicant addresses the double patenting rejection by reiterating the arguments presented against the obviousness rejection above. These arguments were addressed above, and the rejection is maintained for the reasons set forth above.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.

DAVE TRONG NGUYEN
PRIMARY EXAMINER